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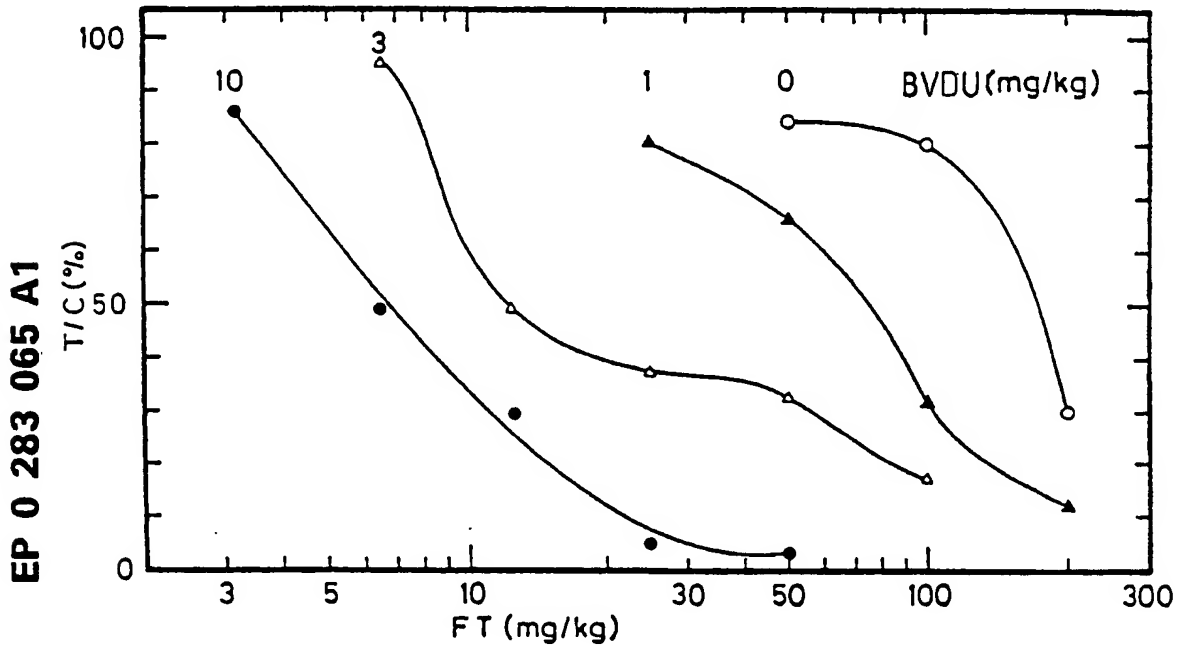
(71) Applicant: Stichting REGA V.Z.W.
Minderbroedersstraat 10
B-3000 Leuven(BE)

(72) Inventor: De Clercq, Erik
Rega Instituut Minderbroedersstraat 10
B-3000 Leuven(BE)
Inventor: Iigo, Masaaki
National Cancer Center Research Inst.
Tsukiji 5-1-1, Chuo-ku Tokyo 104(JP)

(74) Representative: Bruin, Cornelis Willem et al
OCTROOIBUREAU ARNOLD & SIEDSMA
Sweelinckplein 1
NL-2517 GK The Hague(NL)

(54) Combinations of FU and BVU as anti-adenocarcinoma agents.

(57) The antitumor activity of 5-fluorouracil and its precursors against adenocarcinomas can be potentiated without a corresponding increase in toxicity by combining these compounds with (E)-5-(2-bromovinyl)-uracil or a precursor thereof. The combinations may have the form of a single composition or two separate compositions.



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Combinations of FU and BVU as anti-adenocarcinoma agents.

This invention relates to an antitumor agent having activity against adenocarcinoma tumors and being based upon a combination of a well-known antitumor agent with an activity-potentiating agent.

The compound 5-fluorouracil (abbreviated FU) is a well-known antitumor agent used in the treatment of various cancers, in particular adenocarcinomas of the breast and gastrointestinal tract. The margin between activity and toxicity of FU is, however, very narrow and moreover, FU is degraded rather rapidly in the liver.

In some countries, ftorafur (abbreviated FT), i.e. N.-(2'-tetrahydrofuryl)-5-fluorouracil is used instead of FU. Ftorafur has a similar activity as FU and a lower toxicity since it is converted slowly to FU in the human body. Nevertheless, the margin between activity and toxicity of ftorafur is still narrow and thus, there exists a need for agents having a wider margin in this respect.

During experiments which led to the invention, it has now been found that the antitumor activity of FU or FT against adenocarcinomas may be potentiated without a corresponding increase in toxicity by combining this compound with (E)-5-(2-bromovinyl)-2'-deoxyuridine (abbreviated BVDU).

BVDU is a potent and selectively acting antiviral agent, which in particular is active against infections caused by herpes simplex virus type 1, varicella zoster virus and Epstein-Barr virus. In the human body, it is rapidly converted to 5-(2-bromovinyl)uracil (abbreviated BVU) which remains present in the blood stream for a relatively long period. BVU as such is inactive against replication of viruses but it is responsible for the potentiation of the antitumor activities of FU or FT.

When BVDU is combined with FU or FT, the antitumor activity against adenocarcinomas thereof is potentiated substantially whilst the toxicity of FU/FT increases to a lesser degree. This means that the useful margin as well as the therapeutic index of FU/FT increase significantly. In fact, BVU is responsible for this potentiation and therefore, a similar effect will occur with combinations of FU/FT with BVU and with substances other than BVDU that are converted to BVU in the human body. Thus, potentialities are offered for an efficient control of adenocarcinomas in man.

It should be noted that a potentiated activity of FU against leukemia in mice by means of BVU has been disclosed already by Desgranges et al. in Cancer Research, 46, 1094-1101 (1986). However, tests made by Desgranges et al showed that the toxicity of FU was also potentiated by BVU. These data did not allow to presume that the activity of FU/FT against adenocarcinomas would be susceptible of potentiation by BVU without a corresponding increase in toxicity.

The invented agent may be a single therapeutic composition which comprises a combination of FU/FT with BVU (or a precursor of BVU), but it may also comprise two separate compositions which are to be administered in combination, viz. a FU/FT-containing composition and a composition containing BVU or BVU precursor. The compositions may have the form of suspensions, solutions and the like and may be used for oral or parenteral administration. They may be prepared by mixing the active ingredients with pharmaceutically acceptable excipients of inert nature, such as aqueous or non-aqueous solvents together with stabilisers, emulsifiers, additives and the like. The concentration of the active ingredient in any composition may vary between 0.1% and 100%, dependent from the route of administration. The ratio between FU/FT and BVU or BVU-precursor may be between 1:1 and 1:100. Further, the daily dose of the active ingredients to be administered may be between 0.1 mg and 100 mg per kg of body weight.

The invention is further illustrated by the following Examples which are not meant to be restrictive. Reference is made to the drawing which is a graphical representation of the results of Example 2. The abbreviations used are the same as in the preceding description.

The compounds FU and FT as used in the Examples were commercially obtained and the compound BVDU was synthesized according to the method disclosed by Jones et al., Tetrahedron Lettres, 4415-4418 (1979).

Example 1

Groups of 6 male BDF.-mice having a body weight of 21 to 23 g, were subcutaneously inoculated on day 0 with tumor cells of the type adenocarcinoma 755 in a dose of 5×10^6 cells per mouse. Thereupon, the compound FU (or a combination of FU and BVDU) was perorally administered in a predetermined daily dose during 5 consecutive days, starting 24 hours after the inoculation with tumor cells. On day 12, the tumor weight was determined and compared with the tumor weight in a non-treated control group. The doses of the active compounds as used, as well as the average tumor weight and the percentual tumor weight with regard to the control groups (T·C) are represented in the following Table.

Compounds	Mean ± SD (mg)	T/C (%)
Control	2076 ± 364	-
FU , 5 mg/kg	2523 ± 389	122
FU , 10 mg/kg	1759 ± 726	85
FU , 20 mg/kg	675 ± 355	32
FU , 30 mg/kg	Toxic (3/6 died)	
FU, 1 mg/kg + BVDU, 100 mg/kg	1355 ± 561	65
FU, 3 mg/kg + BVDU, 100 mg/kg	486 ± 298	23
FU, 5 mg/kg + BVDU, 100 mg/kg	288 ± 210	14
FU, 10 mg/kg + BVDU, 100 mg/kg	0 ± 0 (1/6 died)	0
FU, 20 mg/kg + BVDU, 100 mg/kg	Toxic (4/6 died)	
FU, 30 mg/kg + BVDU, 100 mg/kg	Toxic (6/6 died)	

From the Table, the following values for the therapeutic index may be calculated, based upon the ratio of LD_{50} (50% lethal dose) to ED_{50} (50% effective dose, that is a dose causing a 50% reduction of T/C):
- For FU when used alone: 30/15 = 2.
- For FU when used in combination with BVDU: 17:1.7 = 10.

This represents a significant increase in therapeutic index of FU.

Example 2

Groups of 6 male BDF. mice having a body weight of 21 to 23 g were subcutaneously inoculated on day 0 with tumor cells of the type adenocarcinoma 755 in a dose of 5×10^5 cells per mouse. Thereupon, combinations of FT with BVDU were perorally administered in a predetermined daily dose during 5 consecutive days, starting 24 hours after the inoculation with tumor cells. The BVDU was used after dissolution in a physiological saline solution and the FT was used after suspension in 0.5% carboxymethyl cellulose solution. A volume of 0.1 ml per 20 g of body weight was used each time for oral administration. The tumor weight was determined on day 12 and compared with that of the control group which had not been treated with the compounds. The results are represented in the drawing, wherein T/C is the procentual ratio of tumor weights in the treated and non-treated groups. The dose of FT has been shown on the abscissa and the doses of BVDU have been indicated at each separate curve.

It appears from the drawing that within the range of doses used (1-10 mg/kg) the antitumor activity of FT was markedly potentiated by BVDU so that a combination of FT at 10 mg/kg with BVDU at 10 mg/kg was as effective as FT alone at 200 mg/kg.

Claims

1. A medicine for use against adenocarcinomas, comprising 5-fluorouracil or a derivative converted in the body to 5-fluorouracil as an active ingredient in combination with (E)-5-(2-bromovinyl)-uracil or a derivative converted in the body to (E)-5-(2-bromovinyl)-uracil.

2. The medicine as claimed in claim 1, which comprises a combination of 5-fluorouracil with (E)-5-(2-bromovinyl)-2'-deoxyuridine.

3. The medicine as claimed in claim 1, which comprises a combination of N,-(2'-tetrahydrofuryl)-5-fluorouracil with (E)-5-(2-bromovinyl)-2'-deoxyuridine.

4. The medicine as claimed in claim 1, which has the form of a single composition.

5. The medicine as claimed in claim 1, which has the form of two separate compositions.

6. The medicine as claimed in claim 1, wherein the ratio between 5-fluorouracil (or its precursor) and (E)-5-(2-bromovinyl)-uracil (or its precursor) is between 1:1 and 1:100.

7. Utilisation of 5-fluorouracil (or a derivative converted in the body to 5-fluorouracil) and (E)-5-(2-bromovinyl)-uracil (or a derivative converted in the body to (E)-5-(2-bromovinyl)-uracil) for preparing a medicine against adenocarcinomas.

Claims for the following Contracting States : ES; and GR

1. A method of preparing a medicine for use against adenocarcinomas, wherein 5-fluorouracil or a derivative converted in the body to 5-fluorouracil as an active ingredient is combined with (E)-5-(2-bromovinyl)-uracil or a derivative converted in the body to (E)-5-(2-bromovinyl)-uracil.

2. The method as claimed in claim 1, wherein 5-fluorouracil is combined with (E)-5-(2-bromovinyl)-2'deoxyuridine.

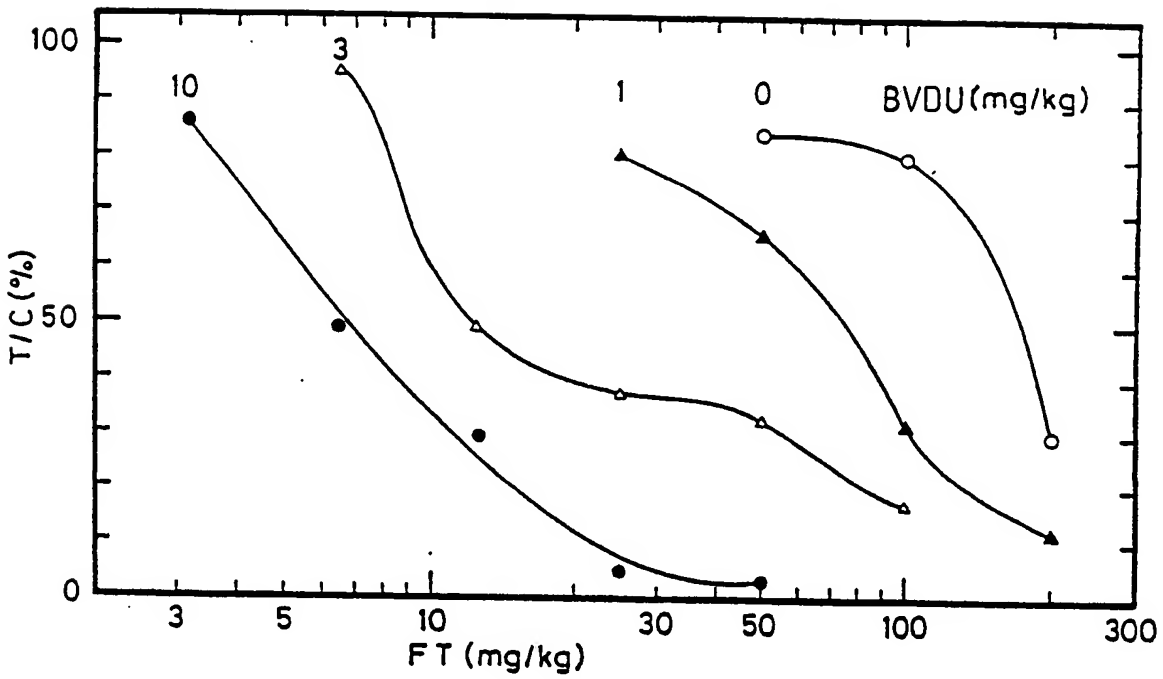
3. The method as claimed in claim 1, whereinN,-(2'-tetrahydrofuryl)-5-fluorouracil is combined with (E)-5-(2-bromovinyl)-2'-deoxyuridine.

4. The method as claimed in claim 1, wherein the resulting product has the form of a single composition.

5. The method as claimed in claim 1, wherein the resulting product has the form of two separate compositions.

6. The method as claimed in claim 1, wherein the ratio between 5-fluorouracil (or its precursor) and (E)-5-(2-bromovinyl)-uracil (or its precursor) is between 1:1 and 1:100.

7. Utilisation of 5-fluorouracil (or a derivative converted in the body to 5-fluorouracil) and (E)-5-(2-bromovinyl)-uracil (or a derivative converted in the body to (E)-5-(2-bromovinyl)-uracil) for preparing a medicine against adenocarcinomas.


100
50
0
T/C (%)
3
10
1
0
BVDU (mg/kg)
3
5
10
30
50
100
300
FT (mg/kg)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 20 0265

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,X	CHEMICAL ABSTRACTS, vol. 104, no. 21, 26th May 1986, pages 25-26, abstract no. 179820h, Columbus, Ohio, US; C. DESGRANGES et al.: "Effect of (E)-5-(2-bromovinyl)uracil on the catabolism and antitumor activity of 5-fluorouracil in rats and leukemic mice", & CANCER RES. 1986, 46(3), 1094-101 * Abstract *	1-7	A 61 K 31/70 // (A 61 K 31/70 A 61 K 31:505)
A	EP-A-0 189 755 (F. HOFFMANN-LA ROCHE & CO.)	1-7	
A	EP-A-0 143 987 (STENDARDI, ANNA GIOIA)	1-7	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	18-05-1988	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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L : document cited for other reasons

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